II. PATENTABILITY ARGUMENTS

A. The Rejection Under 35 U.S.C. § 112, First Paragraph, Should Be Withdrawn.

The Examiner rejected claims 44-65, 78-109, and 145 under 35 U.S.C. § 112, first paragraph, allegedly for failing to comply with the written description requirement. Applicants bring to the Examiner's attention that claim 44 was canceled in the amendment filed on October 10, 2000. Thus, applicants believe that the Examiner inadvertently misstated claim 44 as being rejected.

With respect to rejection of claims 44-65, 78-109 and 145 under 35 U.S.C. § 112, first paragraph, the Examiner alleges that the claims, as amended, contain new subject matter because the newly added limitation ". . . has enzymatic activity when displayed at the surface of filamentous bacteriophage particles" is not supported by the specification as filed.

Applicants respectfully traverse the rejection and submit that newly added limitation is fully supported with specification as filed. For example 12 (at page 59 of the specification, as originally filed), applicants teach that alkaline phosphatase retains its enzymatic activity when displayed at the surface of filamentous bacteriophage particles (see lines 36 through 38 of page 59). Furthermore, the specification discloses a detailed protocol as to how enzymatic activity of an enzyme displayed at the surface of a filamentous bacteriophage particle can be measured. Specifically, lines 4 to 26 of page 59 teach how *E. coli* cells infected with filamentous bacteriophage particles displaying alkaline phosphatase at their surface can be grown and how enzyme activity can be measured. The results of these measurements are show in Table 3 of the specification as

originally filed and demonstrates that alkaline phosphatase, displayed at the surface of filamentous bacteriophage particles, has enzymatic activity.

Support for the limitation is also found in Example 36 (at page 104 of the specification), which demonstrates expression of catalytically active staphylococcal nuclease on the surface of the filamentous bacteriophage fd. Lines 35 to 52 of page 104, provide a detailed protocol as to how the enzymatic activity of a nuclease displayed at the surface of filamentous can be measured by using single stranded DNA as a substrate and then provides data showing that the nuclease retains its enzymatic activity.

In view of the foregoing the Applicants respectfully submit that the claimed limitation ". . . has enzymatic activity when displayed at the surface of filamentous bacteriophage particles" is fully supported by the specification as filed, is not new matter and therefore, the rejection of claims 44-65, 78-109, and 145 under 35 U.S.C. § 112, first paragraph, should be withdrawn and withdrawal is requested.

B. The Rejection Under 35 U.S.C. § 112, Second Paragraph, Should Be Withdrawn.

Claims 45-65, 78-109, 145 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being incomplete for omitting essential steps, such omission amounting to a gap between the steps. The Applicants respectfully traverse the rejection and submit that the allegedly omitted step is inherent in the method. However, in the interest of expediting an already long prosecution, the applicants have amended the claims by adding the phrase "as measured in an enzymatic assay." This amendment is fully supported by the specification as filed. For example, at page 59 of the specification (lines

4 to 38), applicants teach how the enzymatic activity of alkaline phosphatase displayed at the surface of filamentous bacteriophage particles can be measured. On page 104 of the specification as originally filed, applicants teach how the enzymatic activity of staphylococcal nuclease displayed at the surface of bacteriophage particles can be measured.

In view of the forgoing the applicant submit that the rejections under 35 U.S.C. § 112 second paragraph should be withdrawn.

C. The Rejection Under 35 U.S.C. § 102(b) Should Be Withdrawn.

The Examiner rejected claims 46, 48-65, 78-109 and 145 under 35 U.S.C. § 102(b) as allegedly being anticipated by EP 0436597 B1 (Ladner EP). The rejection should be withdrawn because as submitted below, Ladner EP fails to teach each and every element of the instant claims and because the reference has been revoked by the Technical Board of Appeals of the European Patent Office as failing to enable the practice the invention.

In the last sentence of page 6 of the Office Action, the Examiner again erroneously states that Ladner EP discloses "stable BPTI a 58 amino acid with enzymatic activity". However, **BPTI (bovine pancreatic trypsin inhibitor) is not an enzyme and has no enzymatic activity**. The Examiner is directed to page 46, lines 8-9 of Ladner EP which explicitly state that one reason BPTI is chosen for the hypothetical example is that it does not have any enzymatic activity:

> "BPTI is freely soluble and is not know to bind metal ions. BPTI has no known enzymatic activity... BPTI is not toxic."

Thus, Ladner EP explicitly teaches that "BPTI has no known enzymatic activity."

Furthermore, Ladner EP, as discussed previously, explicitly teaches inactivation and mutation to abolish activity of an enzyme if it were to be displayed at the surface of filamentous phage particles and in doing so cannot anticipate the present claims which require the display of an active enzyme on the surface of a filamentous phage. In particular Ladner EP states:

> 2.3. Other consideration in the choice of IPBD:
>
> If the chosen IPBD is an enzyme, it may be necessary to change one or more residues in the active site to inactive enzyme function. For example, **if** the IPBD were T4 lysozyme and the GP were *E.coli* cells or **M13, we would need to inactivate the lysozyme** because otherwise it would lyse the cells. **If**, on the other hand, the GP were **ΦX174**, then **inactivation of lysozyme may not be needed** because T4 lysozyme can be overproduced inside *E.coli* cells without detrimental effects and ΦX174 forms intracellularly. It is preferred to inactivate enzyme IPBDs that might be harmful to the GP or its host by substituting mutant amino acids at one or more residues of the active site. It is permitted to vary one or more of the residues that were changed to abolish the original enzymatic activity of the IPBD. Those GPs that receive osp-pbd genes encoding an active enzyme may die, but the majority of sequences will not be deleterious. (Emphasis added).

In the passage quoted above, Ladner EP first states the general proposition that it may be necessary to inactivate enzyme function if the IPBD is an enzyme. In more specific examples Ladner EP distinguishes different types of genetic packages (GPs): *E.coli* and filamentous phages being two types and non-filamentous phages being another type.

> "If the IPBD were T4 lysozyme [enzyme] and the GP were . . . M13 [filamentous bacteriophage], we would need to inactivate the lysozyme [enzyme]. . . If, on the other hand, the GP were ΦX174 [non-filamentous bacteriophage], then inactivation may not be needed."

The Examiner interprets this passage (in the last sentence on page 9 of the Office Action) as teaching that only harmful enzymes must be inactivated when expressed at the surface of filamentous bacteriophage particles. However, this interpretation alters the plain meaning of Ladner EP disclosure. Contrary to the Examiner's interpretation, Ladner EP explicitly states that when a filamentous bacteriophage is used, an artisan "would need to inactivate..." the enzyme. However, when a non-filamentous bacteriophage is used, an artisan may not need to inactivate the enzyme. Applicants point out that Ladner EP does not provide for conditional inactivation of the enzyme displayed at the surface of a filamentous bacteriophage. In other words, nowhere does Ladner EP state that only if the enzyme is harmful, then artisan needs to inactivate the enzyme. That language is simply not present in Ladner EP. Furthermore, the Examiner misinterpreted the last sentence of paragraph II.D. as teaching that the majority of active enzymatic sequences would not be harmful when expressed at the surface of filamentous bacteriophage particles and therefore, they should not be inactivated. This interpretation is impermissible because it again alters the meaning of Ladner EP disclosure. Applicants respectfully submit that the sentence simply states that GPs that receive "an active enzyme may die, but the majority of sequences will not be deleterious." Contrary to the Examiner's assertion, it does not state that only harmful enzymes should be inactivated. The sentence itself makes the distinction between on the one hand active enzymes and death, and on the other hand other sequences not being deleterious..

The applicants also respectfully submit that the Ladner EP reference does not properly anticipate the instant invention because it fails to disclose the specific combination of features required by the present claim. The instant claims are directed, *inter alia,* to methods of producing any enzyme with enzymatic activity displayed at the surface of a filamentous bacteriophage. It follows that as a matter of law, unless Ladner EP teaches that specific combination. It cannot anticipate the present invention.

As discussed above, Ladner EP does not disclose the combination of displaying an active enzyme at the surface of filamentous bacteriophage particles as presently claimed and contains no experimental exemplification of display of any enzyme. Instead, Ladner EP explicitly selects a molecule that expressly lacks enzyme activity (BPTI) and teaches inactivation if an enzyme is to be displayed at the surface of filamentous bacteriophage particles. In view of the foregoing, Ladner EP cannot properly anticipate the present invention and therefore the rejection should be withdrawn.

In addressing the applicants' prior response, the Examiner cites claim 15 against the instant claims: the position being that claim 15 indicates "display of active enzymes (less active) but not lethal enzymatic activity (relatively less activity) and this "clearly anticipates the claimed invention". However, the applicants respectfully submit that the language of claim 15 does not support the Examiner's interpretation. It recites displaying a binding protein which does not have an enzymatic activity and which is analogous in its sequence to an enzyme whose activity has lethal effect on the amplifiable genetic package. Claim 15 of Ladner EP to which the Examiner refers is as follows:

> 15. The method of claim 5 wherein the known binding protein is an enzyme, the activity of which has a lethal effect on the amplifiable genetic package, the host of the amplifiable genetic package, or the target, wherein the majority of the nucleic acid constructs code on expression for an analogue of the known binding protein that does not have such lethal enzymatic activity.

Claim 15 depends from claim 5:

> 5. The method of claim 1 wherein the parental potential binding domain is initially chosen to be one which is over 50% homologous with a domain of a known protein, the latter domain having a melting point of at least about 60%.

Claim 5 in turn depends on claim 1 which states:

1. A method of obtaining a nucleic acid encoding a proteinaceous binding domain that binds a predetermined target material, other than the antigen combining site of an antibody which specifically binds said domain, comprising:
   (a) preparing a variegated population of amplifiable genetic packages, said genetic packages being selected from the group consisting of cells, spores, and viruses, each said genetic package being genetically alterable and having an outer surface including a genetically determined outer surface protein, each package including a first nucleic acid construct coding for a chimeric potential binding protein, each said chimeric protein comprising, and each said construct comprising DNA encoding,
      i. a potential binding domain which is a mutant of a stable predetermined domain of a predetermined parental protein, other than a single chain antibody, comprising one or more identifiable surface residues, and for which both an affinity molecule and an amino acid sequence are either available or obtainable, and
      ii. an outer surface transport signal for obtaining the display of the potential binding domain on the surface of the genetic package, the expression of which construct results in the display of said chimeric potential binding protein and its potential binding domain on the outer surface of said genetic package; and wherein said variegated population of genetic packages collectively display a plurality of different potential binding domains, the differentiation among said plurality of different potential binding domains occurring through the at least partially random variation of one or more predetermined amino acid positions of said parental binding domain to randomly obtain at each said position an amino acid belonging to a predetermined set of two or more amino acids, the amino acids of said set occurring at said position in statistically predetermined expected proportions, the genetic message encapsulated by said genetic packages being amplifiable *in vitro* or by cell culture of said genetic packages and separable on the basis of the potential binding domain displayed thereon,
   (b) causing the expression of said chimeric potential binding proteins and the display of said potential binding domains on the outer surface of said packages;
   (c) contacting said packages with the predetermined target material such that said potential binding domains and the target material may interact;
   (d) separating packages displaying a potential binding domain that binds the target material from packages that do not so bind, on the basis of their ability to bind with the target material in step (c); and

(e) recovering at least one package displaying on its outer surface a chimeric binding protein comprising a stable successful binding domain (SBD) which bound said target, said package comprising nucleic acid encoding said successful binding domain, and amplifying said SBD-encoding nucleic acid in vivo or in vitro.

Nowhere does claim 15 or its predecessors recite less active enzymes at the surface of a filamentous bacteriophage, it recites: "does not have the lethal enzyme activity."

It is clear from reading these claims that there is no specific disclosure of the combination of display of any enzymatically active enzyme on the surface of filamentous bacteriophage particles. The "genetic packages"(GP) of claim 1, according to Ladner EP, may be selected from cells, spores and viruses. In relation to the single filamentous bacteriophage mentioned in Ladner EP as a possible GP for attempted display of any enzyme, the description teaches "inactivation" and "abolishing" of enzymatic activity – as discussed above.

At page 7 of the Office Action, the Examiner cites In *re Van Geun* for the proposition that although claims are interpreted in light of the specification, limitations from the specification are not read into the claims. In other words, if a scope of a claim at issue is narrower than what is disclosed in the specification, a court will not award an applicant a claim with a broader scope only because the broader scope would be supported by the specification as filed ("limitations from the specification are not read into the claims"). Applicants respectfully submit that regardless of how such claim may be interpreted, the law requires that the prior art must teach each and every element of the claimed invention. Ladner EP does not. The present claims recite the display of active enzymes on the surface of filamentous phage. Ladner EP as discussed in more detail

above, does not teach the invention as presently claimed. Ladner EP specification provides that enzymes are inactivated when presented at the surface of filamentous bacteriophage (see above).

In summary, because Ladner EP does not teach combination of each and every element of the present claims, it cannot properly anticipate the present invention.

Ladner EP Fails to Enable the Practice of the Present Invention

Even if Ladner EP were to disclose the combination of each and every element as presently claimed, it cannot anticipate the instant claims because the reference has been determined to be inoperative (non-enabling) by the European Patent Office and the patent has been revoked on that basis.

In order to anticipate a claim, a reference must, *inter alia*, enable one skilled in the art to practice the claimed invention. *Titanium Metals Corp. of America v. Banner*, 778 F.2d 775, 778, 227 U.S.P.Q. 773 (Fed. Cir. 1985). ("A reference is not an anticipation which does not enable one skilled in the art to practice the claimed invention.")

The issue of enablement of Ladner EP was addressed at the European Patent Office (EPO) Technical Board of Appeals (the "Board") (the highest level of technical review at the European Office and not subject to further review) in its decision T0792/00 ("Reasons for Decision," attached hereto) which affirmed the completely non-enabling nature of the Ladner EP disclosure even with respect to its narrowest claim 29 when it upheld the decision of the Opposition Division of the European Patent Office to **revoke**

the Ladner EP patent. A copy of the decision was attached with applicants' previous response. In their decision, the Board wrote:

> **In other words, the patent in suit itself casts strong doubts on the possibility to perform the claimed object.** Furthermore, since every element of the solution proposed in the patent in suit (i.e., signal sequence, outer surface protein, genetic package) may be, according to the sentence of the patent in suit (page 52, lines 7 to 9), a potential source of failure, the patent in suit does not provide the skilled person with a real guidance to perform the claimed subject-matter but on the contrary, in the Board's view, offers nothing else to the skilled person than an outline of a search programme. An invention, however, is supposed to relate to a solution to a technical problem. First to perform a research programme that the patentee has outlined but not himself performed, and for which the prospects of success appear poor, is not a burden that can be put on a skilled person trying to reproduce an invention. (Emphasis added.)

The Examiner argues that the Board's decision was with respect to claim 29 which is the narrowest claim and which does not have the same limitations as those claimed in the instant application. First of all, if the Board found that Ladner EP failed to enable with respect to even what the Examiner characterized as the narrowest claim, then it logically follows that Ladner EP does not enable any other of its claims either.

Claim 29 of Ladner EP reads as follows:

> A chimeric protein comprising (i) at least a segment of an outer surface protein of a filamentous phase, said segment providing an outer surface transport signal recognized by a cell infected by said phage such that the chimeric protein is assembled into the coat protein of phage particles produced by said cell, and (ii) a stable proteinaceous binding domain, other than a single chain antibody, said domain comprising one or more identifiable surface residues, that binds a predetermined target material, other than the antigen combining site of an antibody which specifically binds said domain, the target being bound sufficiently strongly so that the dissociation constant of the binding domain: target complex is less than 10^{-6} moles/ liter, and that is heterologous to said phage.

As quoted above, the Board stated that every element of the solution proposed in the patent-in-suit (i.e. signal sequence, outer surface protein, genetic package...) may be a source of failure, the patent-in-suit does not provide the skilled person with a real guidance to perform the claimed subject matter. In view of the Board having determined that **every element** of the solution (display of chimeric protein on surface of a filamentous phage) may be a source of failure the applicants respectfully submit that nothing from Ladner *et al.* may be salvaged so as to anticipate the present invention which involves the display of active enzymes on the surface of filamentous phage. Simply stated the Board has determined that **Ladner EP does not enable display of anything on the surface of filamentous phage**, let alone the display on the surface of filamentous bacteriophage particles a polypeptide which is a specific binding pair member capable of binding a complementary ligand ... a specific binding pain member which comprises an enzyme or fragment thereof having enzymatic activity ... as is required by the present claim, and therefore the reference cannot properly anticipate the present invention. The applicants respectfully submit that the European Patent Office's finding that Ladner EP does not provide an operable way to display proteins on the surface of a genetic package, (fails to enable the display of proteins) based on factual evidence presented during opposition to the patent satisfies their burden of proof under *In re Sasse* that Ladner EP is non-enabling. On that basis the applicants respectfully submit that Ladner EP cannot properly anticipate the present invention and therefore the rejections should be withdrawn.

In further support of the findings of the Board, the applicants submit herewith the Declaration of Dr. Ronald Henry Jackson, an inventor of the presently claimed invention

who has over 20 years of experience in protein engineering including significant experience with display of antibodies, enzymes and receptors on the surface of bacteriophage. A copy of Dr. Jackson's curriculum vitae is attached hereto as Exhibit A.

In his declaration Dr. Jackson states that he reviewed Ladner EP, the Decision of the Technical Board of Appeals of the European Patent Office T 0792/00-3.3.4, which upheld the Decision of the Opposition Division of the European Patent Office revoking Ladner EP, (which decision was also reviewed by Dr. Jackson), and the supporting factual testimony including the supporting declarations of experts in the field of bacteriophage display. Based on his review of the foregoing, and based on his knowledge of the field of bacteriophage display of proteins at the time of filing of the Ladner EP application, Dr Jackson, in agreement with the Board, concluded that Ladner EP does not provide an operable way of displaying proteins, let alone active enzymes on the surface of filamentous bacteriophage but rather provides nothing more than an outline for further research. Further Dr. Jackson states that Ladner EP does nothing to overcome the prejudice in the art against display of protein over a certain size on the surface of the bacteriophage.

In view of the Board's decision and Dr. Jackson's declaration, each of which independently meet the applicant's burden of proof under *In re Sasse* the applicants submit that Ladner EP is non-enabling and thus cannot properly anticipate the present invention and, therefore, the rejection should be withdrawn.

D. <u>The Rejections Under 35 U.S.C. § 102 (e) Should Be Withdrawn.</u>

The Examiner has rejected claims 46, 48-65, 78-109 and 145 under 35 U.S.C. § 102(e) as allegedly being anticipated by US Patent 5,223,409 (LADNER US).

At page 9 of the office action, the Examiner reiterates the assertion that the applicants do not provide the written description support for applicants' claim limitation "has enzymatic activity when displayed at the surface of filamentous bacteriophage particles" and also because "the instantly claimed method does not recite the required step to determine that the enzyme has enzymatic activity." However, as discussed in detail, section II A above, the amendment "has enzymatic activity when displayed at the surface of filamentous bacteriophage particles" is fully supported by the instant specification as originally filed (see e.g., Examples 12 and 36 of the specification). Further the claims also, as currently amended recite "as measured in an enzymatic assay."

With respect to Examiner's contention that LADNER US teaches display of active enzymes at the surface of filamentous bacteriophage particles), applicants reiterate that in column 23, LADNER US teaches that an enzyme must be inactivated when displayed at the surface of the filamentous phage M13:

> II.D. Other consideration in the choice of IPBD:
>
> If the chosen IPBD is an enzyme, it may be necessary to change one or more residues in the active site to inactive enzyme function. For example, **if** the IPBD were T4 lysozyme and the GP were *E.coli* cells or **M13, we would need to inactivate the lysozyme** because otherwise it would lyse the cells. **If**, on the other hand, the GP were **ΦX174**, then **inactivation of lysozyme may not be needed** because T4 lysozyme can be overproduced inside *E.coli* cells without detrimental effects and ΦX174 forms intracellularly. It is preferred to inactivate enzyme IPBDs that might be harmful to the GP or its host by substituting mutant amino acids at one or

> more residues of the active site. It is permitted to vary one or more of the residues that were changed to abolish the original enzymatic activity of the IPBD. Those GPs that receive osp-pbd genes encoding an active enzyme may die, but the majority of sequences will not be deleterious. (Emphasis added).

The Examiner again erroneously states that Ladner US discloses "stable BPTI a 58 amino acid with enzymatic activity". However, **BPTI (bovine pancreatic trypsin inhibitor) is not an enzyme and has no enzymatic activity**. The Examiner is directed to columns 23 and 24 of Ladner US which explicitly state that one reason BPTI is chosen for the hypothetical example is that it does not have any enzymatic activity:

> "BPTI is freely soluble and is not know to bind metal ions. BPTI has no known enzymatic activity. BPTI is not toxic."

Thus, Ladner US explicitly teaches that "BPTI has no known enzymatic activity."

Furthermore, LADNER US (as does Ladner EP) as discussed above, explicitly teaches "inactivation" and mutation to "abolish" enzymatic activity of the enzyme if it were to be displayed at the surface of filamentous phage particles and in doing so cannot anticipate the present claims which require the display of an active enzyme on the surface of a filamentous phage. In particular Ladner US states:

> II.D. Other consideration in the choice of IPBD:
>
> If the chosen IPBD is an enzyme, it may be necessary to change one or more residues in the active site to inactive enzyme function. For example, **if** the IPBD were T4 lysozyme and the GP were *E.coli* cells or **M13, we would need to inactivate the lysozyme** because otherwise it would lyse the cells. **If**, on the other hand, the GP were **ΦX174**, then **inactivation of lysozyme may not be needed** because T4 lysozyme can be overproduced inside *E.coli* cells without detrimental effects and ΦX174 forms intracellularly. It is preferred to inactivate enzyme IPBDs that might be harmful to the GP or its host by substituting mutant amino acids at one or more residues of the active site. It is permitted to vary one or more

> of the residues that were changed to abolish the original enzymatic activity of the IPBD. Those GPs that receive osp-pbd genes encoding an active enzyme may die, but the majority of sequences will not be deleterious. (Emphasis added).

LADNER US first states the general proposition that it may be necessary to inactivate enzyme function if the IPBD is an enzyme. In more specific examples LADNER US distinguishes different types of genetic packages (GPS): *E.coli* and filamentous phages being two types and non-filamentous phages being another type.

> "If the IPBD were T4 lysozyme [enzyme] and the GP were . . . M13 [filamentous bacteriophage], we would need to inactivate the lysozyme [enzyme]. . . If, on the other hand, the GP were ΦX174 [non-filamentous bacteriophage], then inactivation may not be needed."

The Examiner again interprets this passage as teaching that only harmful enzymes must be inactivated when expressed at the surface of filamentous bacteriophage particles. However, this interpretation alters the meaning of the LADNER US disclosure. Contrary to the Examiner's interpretation, Ladner EP explicitly states that when a filamentous bacteriophage is used, an artisan "needs to inactivate" the enzyme. However, when a non-filamentous bacteriophage is used, an artisan may not need to inactivate the enzyme. LADNER US does not provide for conditional inactivation of the enzyme displayed at the surface of a filamentous bacteriophage. In other words, nowhere does the reference state that only if the enzyme is harmful, then artisan needs to inactivate the enzyme. That language is simply not present in LADNER US. Furthermore, the Examiner misinterpreted the last sentence of the passage as teaching that the majority of active enzymatic sequences would not be harmful when expressed at the surface of filamentous bacteriophage particles and therefore, they should not be inactivated. This interpretation is impermissible because it again alters the meaning of the disclosure. The

sentence simply states that GPs that have "an active enzyme may die, but the majority of sequences will not be deleterious". Contrary to the Examiner's assertion, it does not state that only harmful enzymes should be inactivated. The sentence itself makes the distinction between on the one hand active enzymes and death, and on the other hand other sequences not being deleterious. The issue of enzyme inactivation was not discussed in the sentence, it was discussed earlier in the passage, wherein Ladner EP explicitly teaches that "If . . . GP . . . were M13 [filamentous bacteriophage], we would need to inactivate the lysozyme [enzyme]. . . If, on the other hand, the GP were ΦX174 [non-filamentous bacteriophage], then inactivation may not be needed.

Contrary to the Examiner's assertion, it does not state that only harmful enzymes should be inactivated. The issue of enzyme inactivation was not discussed in the sentence, but was discussed earlier in the passage, wherein Ladner EP explicitly teaches that "If . . . GP . . . were M13 [filamentous bacteriophage], we would need to inactivate the lysozyme [enzyme]. . . If, on the other hand, the GP were ΦX174 [non-filamentous bacteriophage], then inactivation may not be needed."

The applicant also respectfully submit that the LADNER US may not properly anticipate the instant invention because it fails to teach the specific combination of elements required by the present claim. The instant claims are directed, *inter alia,* to methods of producing any enzyme with enzymatic activity displayed at the surface of a filamentous bacteriophage.

As discussed above, LADNER US does not disclose the combination of displaying an active enzyme at the surface of filamentous bacteriophage particles as presently claimed and contains no experimental exemplification of display of any

enzyme. Instead, the reference teaches that if an enzyme is to be displayed at the surface of filamentous bacteriophage particles, the enzyme must be inactivated. Consequently, Ladner cannot properly anticipate the present invention.

In addition to failing to teach displaying active enzymes at the surface of filamentous bacteriophage particles as is called for by the present claim, the reference fails to teach measuring enzyme activity as is required by the currently amended claims. Because a reference may not anticipate the instant claims UNLESS the reference teaches each and every element as instantly claimed, LADNER US does not anticipate the instant claims and therefore, the rejection over claims 46, 48-65, 78-109 and 145 under 35 U.S.C. § 102(e) should be withdrawn and the withdrawal is requested.

E. <u>The Rejections Under 35 U.S.C. § 103(a) Should Be Withdrawn.</u>

The Examiner rejected claims 45-65, 78-109 and 145 under 35 U.S.C. § 103(a) as allegedly being obvious over Ladner EP or LADNER US. Applicants reiterate for reasons set out above that Ladner EP is non-enabling for the display of anything and thus cannot render obvious the present invention. Further more, the instant claims are not obvious in view of Ladner EP even if Ladner EP were held to be operable because Ladner EP neither teaches nor suggests all of the elements of the instant claims. Instead, Ladner EP (as does LADNER US) teaches that if an enzyme were to be displayed at the surface of filamentous bacteriophage particles, the enzyme must be inactivated. Therefore, Ladner EP teaches away from displaying active enzymes at the surface of filamentous bacteriophage particles and as such may not render the instant invention obvious as a matter of law.

As regarding LADNER US, on page 12 of the Office Action, the Examiner rejects applicants' statements that LADNER US teaches away "since applicants have not specifically pointed out which parts of the reference disclosure is teaching away". In response applicants again bring to the Examiner's attention column 23, in LADNER US that teaches inactivation enzyme must be inactivated when displayed at the surface of the filamentous phage M13:

> II.D. Other consideration in the choice of IPBD:
>
> If the chosen IPBD is an enzyme, it may be necessary to change one or more residues in the active site to inactive enzyme function. For example, **if** the IPBD were T4 lysozyme and the GP were *E.coli* cells or **M13, we would to inactivate the lysozyme** because otherwise it would lyse the cells. If, on the other hand, the GP were ΦX174, then inactivation of lysozyme may not be needed because T4 lysozyme can be overproduced inside *E.coli* cells without detrimental effects and ΦX174 forms intracellularly. (Emphasis added).

Thus, LADNER US teaches away from displaying active enzymes at the surface of filamentous bacteriophage particles such as e.g., M13, and therefore cannot render the present invention obvious.

In view of the non-enabling nature of Ladner EP, the teaching against the display of enzymes having enzymatic activity on the surface of filamentous phage as discussed in Ladner EP and LADNER US, applicants respectfully submit that neither Ladner EP nor LADNER US alone or in combination can properly render the present invention obvious and therefore, the rejections of claims 45-65, 78-109 and 145 under 35 U.S.C. § 103(a) should be withdrawn and such withdrawal is requested.

Conclusion

In view of the foregoing amendments and remarks, applicants respectfully submit that the claims are now in condition for allowance and early notification thereof is earnestly solicited.

Respectfully submitted,

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